

# ASSESSMENT ON EFFECTIVENESS OF INTRAVENOUS THROMBOLYSIS IN ENDOVASCULAR RECANALIZATION THERAPY: A RETROSPECTIVE COHORT STUDY

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## ABSTRACT

**Background:** Acute ischemic stroke (AIS) along with haemorrhagic stroke are the most debilitating cardiovascular events in need of rapid medical treatment<sup>1</sup>. Until recent years primary treatment for acute ischemic stroke caused by large vessel occlusion (LVO) was medical management i.e. administration of intravenous thrombolysis. Currently it is under debate whether mechanical thrombectomy (MT) alone or MT combined with intravenous thrombolysis (IVT) provide best treatment results. This investigation assessed effectiveness of IVT combined with MT in recanalization results for ischemic stroke caused by anterior circulation LVO.

**Method:** 139 patient cases treated for anterior circulation ischemic stroke at Turku University Hospital in a two-year period were retrospectively evaluated by recanalization results and patient recovery outcome. The patient cases were divided into groups based on treatment received: MT only and IVT + MT -groups. All patient -cases acted as the control group. Statistical analysis included subdivision of groups by percentiles in each category under assessment. Margin for statistical significance was considered a minimum difference of 10% between the groups.

**Results:** None of the categories under assessment exhibited the margin for statistical significance between the groups. Most substantial differences were obtained within the procedure time categories: > 180 min (9.0% lower for IVT + MT) and 61 – 180 min (5.8% lower for MT).

**Conclusion:** The investigation demonstrates similar results to other research conducted i.e. there exists no definite consensus on the non-inferiority of MT only treatment compared to the combination of IVT + MT when possible (no contraindications present). It is to be acknowledged that further conclusions require more profound statistical analyses as the research data was processed merely with percentile division and preferably consisting of a larger patient case cohort.

**Keywords:** Ischemic stroke, large vessel occlusion, intravenous thrombolysis, mechanical thrombectomy

**Abbreviations:** AIS = acute ischemic stroke, LVO = large vessel occlusion, MT = mechanical thrombectomy, IVT = intravenous thrombolysis, mRS = modified rankin scale

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<sup>1</sup> [Mortality and global health estimates \(WHO.int\)](https://www.who.int)

## 1. Introduction

Stroke is globally the second leading cause of death<sup>2</sup> and major cause of disability. Its incidence is due to cumulate as world population ages and life expectancy increases. Ischemic stroke is more frequent but haemorrhagic stroke results in more deaths and disability-adjusted-life-years lost (DALYs)<sup>3</sup>.

Consensus on treatment for acute ischemic stroke (AIS) caused by proximal anterior circulation large vessel occlusion (LVO) was primarily intravenous thrombolysis (IVT) until 2015 when five<sup>4</sup> significant studies on endovascular recanalization therapy consisting of mechanical thrombectomy (MT) were published.

MR CLEAN Investigators -study demonstrated the efficacy and safety of mechanical thrombectomy within 6 hours of symptom onset in proximal anterior circulation LVO. A significant difference of 13.5% (32.6% vs. 19.1%) was observed in the rate of functional independence (three months post-treatment mRS score 0-2) amongst patients treated with MT compared to IVT alone. No significant difference was observed in mortality nor symptomatic intracerebral haemorrhage (sICH).

Pienimäki J-P., Ollikainen J. etc.<sup>5</sup> demonstrated IVT + MT -group patients had 2.6-fold higher odds of poorer mRS score compared to MT only -group. The two groups had a difference of 22% (60% vs. 38%) in excellent clinical outcome (mRS score 0-1) and 10% difference (16% vs. 6%) in mortality (mRS score 6). There were no significant differences in process times, mTICI or incidence of haemorrhagic complications between IVT + MT and MT only -groups. A trend of less distal embolization and higher number of device passes was observed among MT only -patients.

JAMA -investigations<sup>6</sup> concluded non-inferiority of endovascular treatment alone compared to combination treatment for ischemic stroke caused by proximal anterior circulation occlusion. MT alone -patients achieved functional independence at 90-day follow up (mRS score 0-2) with 7.7% difference to combined treatment patients (54.3% vs. 46.6%, for non-inferiority  $p = 0.03$ ).

A META-analysis<sup>5</sup> of the five studies demonstrated that MT is an effective and safe treatment for proximal anterior circulation LVO in most patient groups.

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<sup>2</sup> [Mortality and global health estimates \(WHO.int\)](#)

<sup>3</sup> [Global Burden of Stroke, M. Katan, A. Luft](#)

<sup>4</sup> [MR CLEAN Investigators, ESCAPE Trial Investigators, REVASCAT Trial Investigators, EXTEND-IA Investigators](#)

<sup>5</sup> [In-Hospital Intravenous Thrombolysis Offers No Benefit in Mechanical Thrombectomy in Optimized Stroke Center Setting \(2020\), Pienimäki J-P., Ollikainen J., Sillanpää N., Protto S.](#)

<sup>6</sup> [Effect of Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke, W. Zi, Z. Qiu et al., 2021](#)

## 1.1 Background on LVO and treatment

80 – 90% of LVOs occur in the anterior circulation (Carotis interna + media and their respective collaterals) and 10 – 20% in the posterior (vertebrobasilar) circulation<sup>7</sup>. Anterior circulation LVO may result in substantial cerebral tissue impairment. Hence treatment emphasizes with good reason on anterior circulation occlusions.

Intravenous thrombolysis therapy alone is efficient only in 10% of the Carotis interna and 30 – 40% media occlusions<sup>5</sup>. In addition, 4.5 hours after symptom onset effectiveness of i.v. thrombolysis decreases, and risk of potential side-effects increases.

Current guidelines include a 6-hour symptom onset time window in which intravenous thrombolysis is to be administered alongside mechanical thrombectomy treatment. Beyond the 6-hour time window ad 24 hours after symptom onset, mechanical thrombectomy plus best medical management without contraindication is recommended<sup>8</sup>.

Contraindications for i.v. thrombolysis include patients' anticoagulation treatment in therapeutic range, recent major surgical operations, and previous intracranial haemorrhages, as all these increase risk of further haemorrhaging<sup>5</sup>.

Mechanical thrombectomy is recommended as treatment in anterior circulation occlusions when collateral vessel reperfusion is seen possible and satisfactory clinical recovery is expected. Complications regarding MT are vessel perforation or dissection, intravascular relocation or reformation of thrombosis, vasospasm, intracranial or subarachnoid space haemorrhages<sup>5</sup>.

## 2. Methods

An observational retrospective study on effect of intravenous thrombolysis (IVT) preceding mechanical thrombectomy (MT) in recanalization results was conducted on patients treated for acute ischemic stroke (AIS) caused by anterior circulation large vessel occlusion (LVO) in TYKS<sup>9</sup> between January 2018 and December 2019. All patients were admitted from the emergency room as MT candidates based on findings provided by preliminary neurological examination and CT imaging of cerebral circulation.

156 patient cases were initially analysed and cases not meeting inclusion criteria were naturally excluded. Exclusion criteria consisted of:

- 1) Unsuccessful MT procedure or recanalization due to patient dependent factors e.g. aberrant vascular anatomy or overall health untenable for procedure
- 2) Non-existent LVO i.e. symptoms caused by other etiology
- 3) Posterior circulation occlusion

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<sup>7</sup> [Thrombectomy presentation, R. Rautio, 2019](#)

<sup>8</sup> [European Society for Minimally Invasive Neurological Therapy Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke, European Stroke Journal 2019](#)

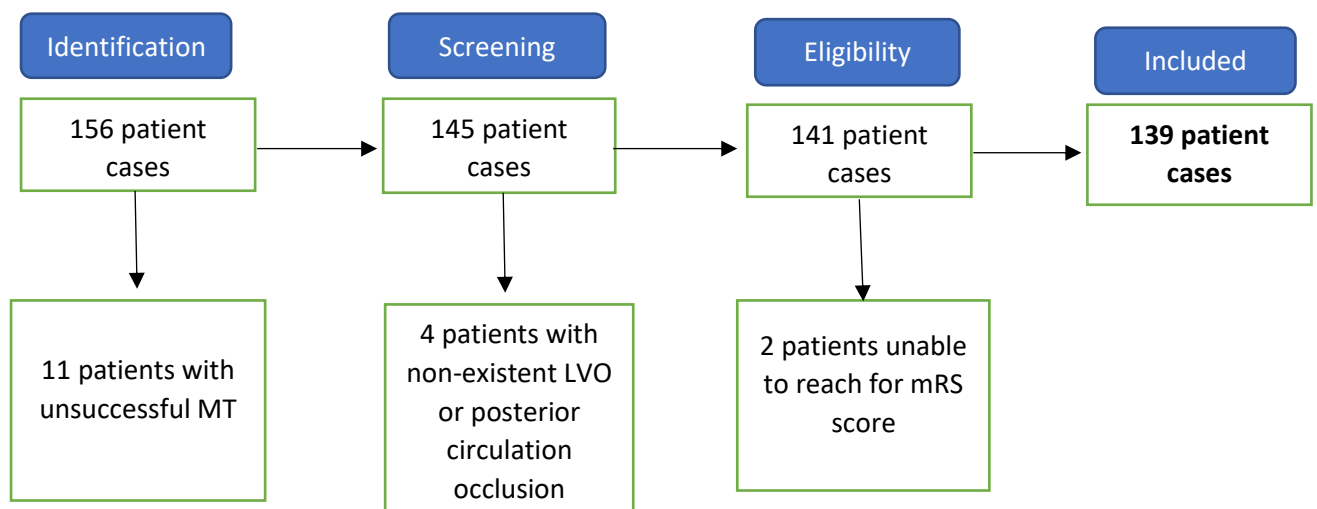
<sup>9</sup> [Turku University Hospital](#)

#### 4) Unobtained data of variables under investigation.

In total 139 patient cases met the inclusion criteria. Patients were divided into two groups based on treatment received: MT alone, n = 62 (44.6%) or IVT + MT, n = 77 (55.4%). Data of all patient cases included in the study (n = 139) regardless of treatment received acted as the control group.

Differences between the two patient groups under investigation were assessed on recanalization attempts required, endovascular devices required for recanalization, puncture to recanalization -time, mRS score and incidence of sICH.

Patient demographics shown in Table 1. included subdivision by gender, age group and smoking. Recanalization attempts required (Fig. 2) were recorded as either single or several. A single attempt could include use of multiple endovascular devices if operated within a single recanalization attempt. Devices for recanalization (Fig. 3) were aspiration or retriever used alone or a combination of these operated through a single catheter. Puncture to recanalization -time (i.e. procedure time) was divided into four different time intervals (Fig 4.) and mRS score was recorded three months post-treatment with an emphasis on asymptomatic results (0-2). Symptomatic intracerebral haemorrhages (sICH) were observed from t = 0 (post operation) up to three months.



**Fig. 1** Flowchart showing patient exclusion process

Characteristic	All Patients n = 139	MT n = 62	IVT + MT n = 77
Male (%)	54.0	54.8	53.2
Female (%)	46.0	45.2	46.8
Age (y) mean	71.4	73.9	69.0
≤ 65 (%)	27.3	19.4	33.8
66 – 80 (%)	47.5	48.4	46.8
> 80 (%)	25.2	32.3	19.5
Smoking (%)	23.1	19.2	23.9

**Table 1.** Showing patient demographics

## 2.2 Statistical analyses

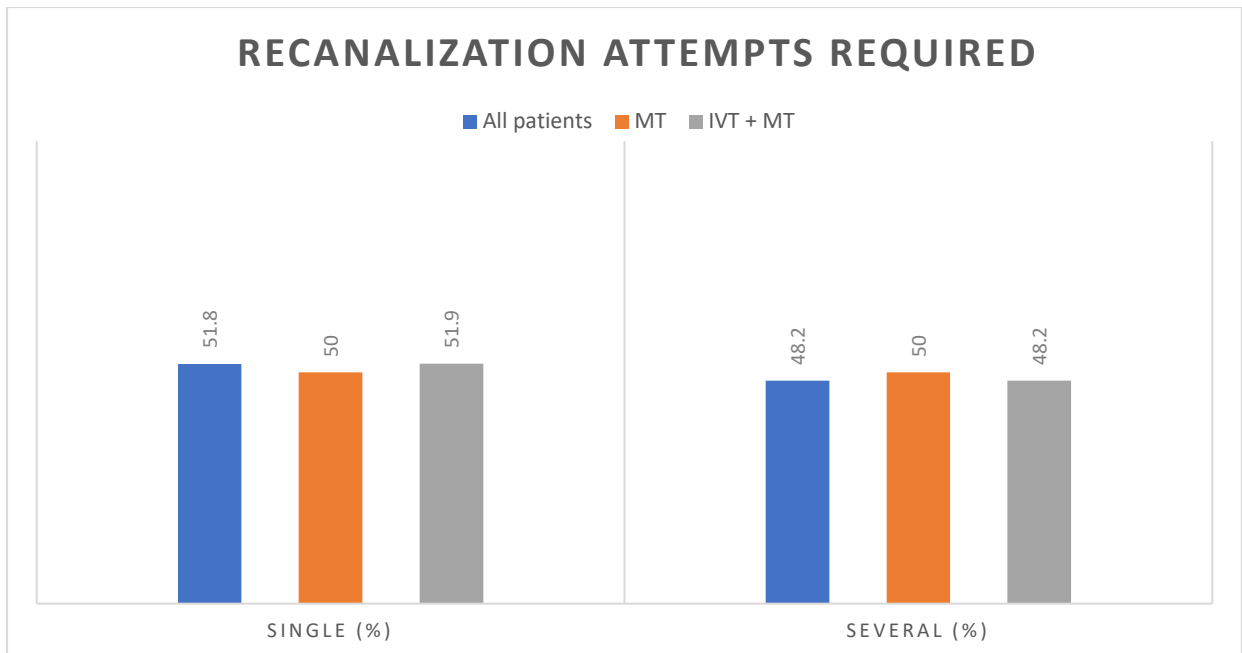
Preliminary statistical analysis of data was performed by computing percentages for each category under investigation within the patient groups. Further analyses including determined statistical values are required for more profound evaluation of investigation results. Nevertheless, in this investigation setting an approximate level of statistical significance was considered a difference margin of a minimum of 10% between the groups.

## 3. Results

Patient demographics show even gender distribution within the groups with a slight majority of males (most difference 54.8% vs. 45.2% in MT only -group, illustrating men have more often contraindications for IVT treatment). Higher representation of males corresponds to the common motif that females in general live longer and healthier than their male counterparts.

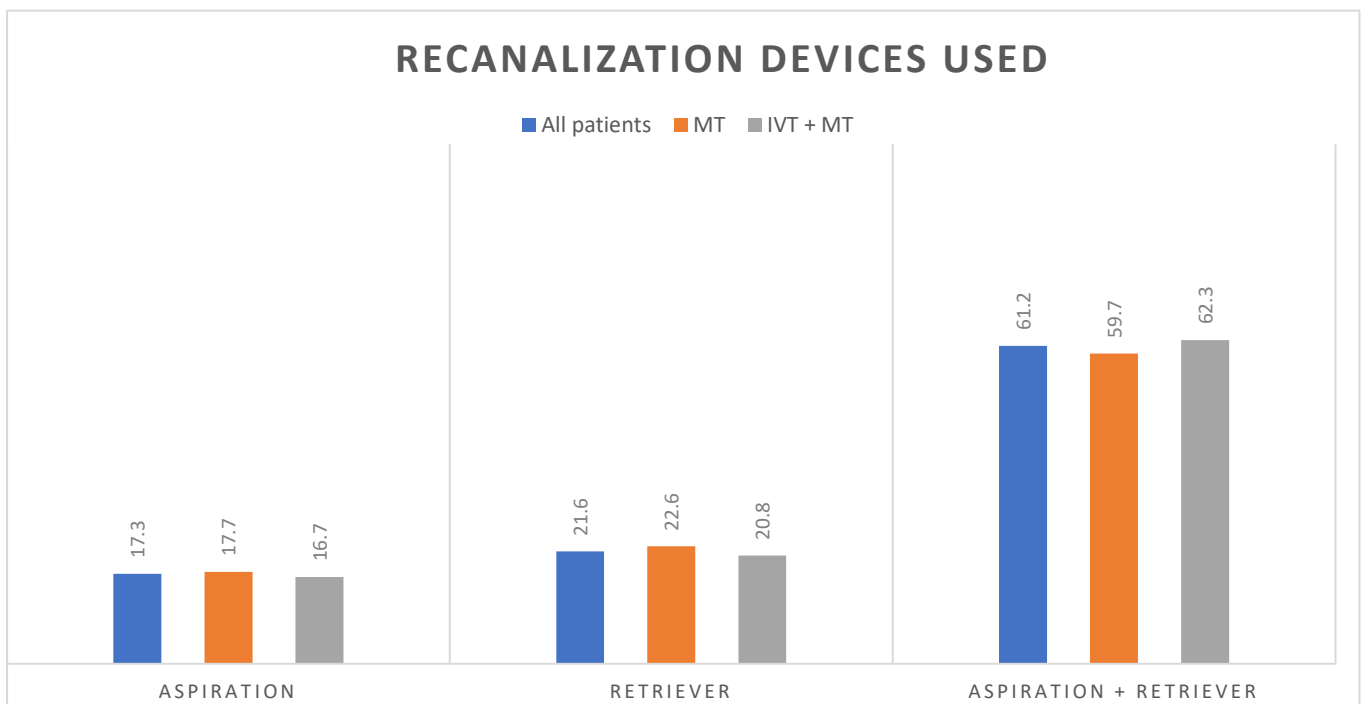
Mean age of patients was  $71 \pm 3$  years (ranging from 69.0 to 73.9) with the most significant subcategory being 66 – 80 years (all patients 47.5%, MT 48.2%, IVT + MT 46.8%). Most substantial variation can be seen in the ≤ 65-year-old patient group: all patients 27.3%, MT 19.4% vs. IVT + MT 33.8% (14.4% difference). This indicating that significantly less patients in the ≤ 65-year-old group had contraindications (e.g. anticoagulation treatment in therapeutic range) for IVT treatment.

Nearly one fourth of all patients were current smokers, with the largest representation in the IVT + MT -group (23.9%).



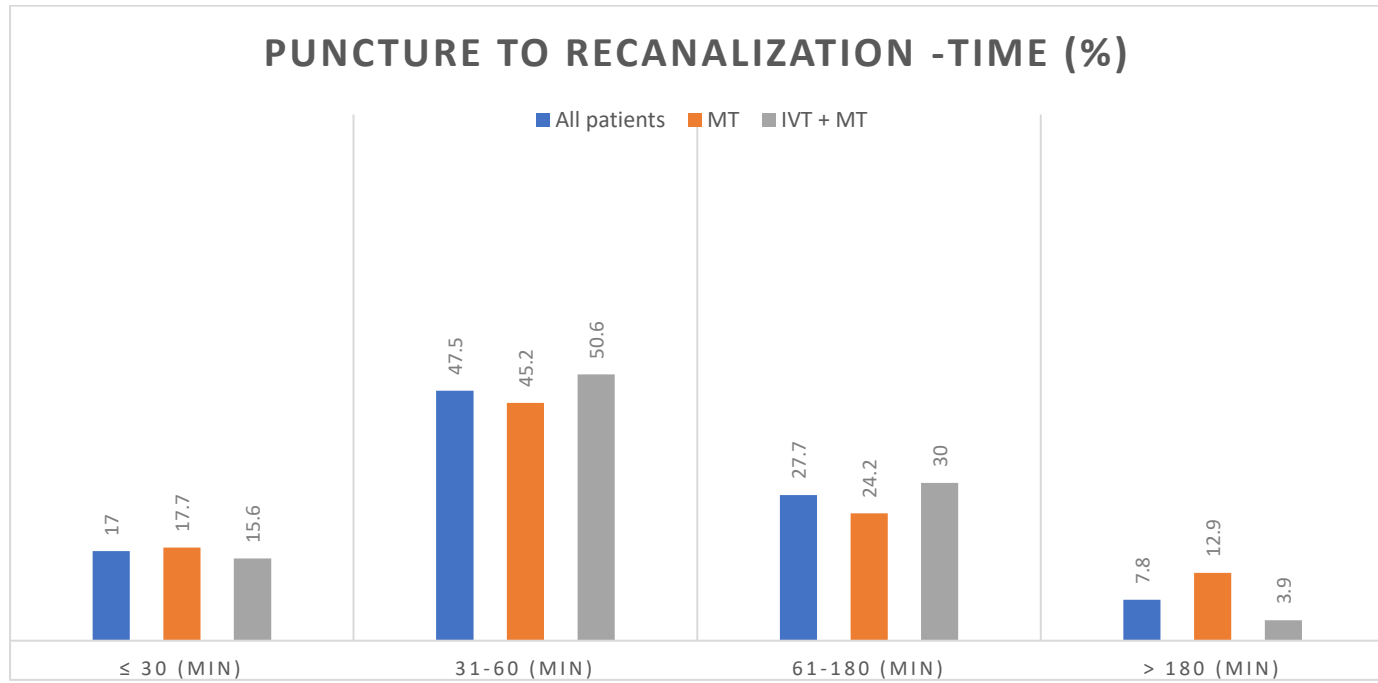
**Fig. 2** Column chart showing attempts required for recanalization

Statistics show no significant difference in the attempts required for recanalization between the groups, with MT only- group having an even 50-50 distribution. Division basis for attempts required was the following: use of multiple endovascular devices (aspiration + retriever) was considered a single attempt when operated through the same catheter in a single session.



**Fig. 3** Column chart displaying devices required for recanalization

Vast majority (up to 62.3% in IVT + MT -group) of recanalization procedures in all groups required use of both aspiration and retriever. Difference between the MT and IVT + MT -groups was merely 2.6%. Choice of recanalization device (i.e. technique used) depends on factors such as preference of the operator and patient case under procedure.



**Fig. 4** Column chart showing puncture to recanalization -time distribution between groups

Procedure time (min)	All patients	MT	IVT + MT
Mean	58	64	54
Median	48	53	49
Minimum	8	11	8
Maximum	230	230	152

**Table 2.** showing procedure time statistics

Fig 4. illustrates that in all groups the procedure time in majority of cases sets within the 31 to 60 min interval with a 5.4% difference (50.6% vs. 45.2%) between the IVT + MT and MT only -group. The 61 – 180 min procedure time -category had a majority of IVT + MT -patients (30.0% vs. 24.2%) with a difference of 5.8%. On the contrast, there exists a 9.0% difference and lower representation of IVT + MT -patients (12.9% vs. 3.9%) within the > 180 min -category.

It is also notable that the IVT + MT -group has the lowest mean value for procedure time (54 min) with a difference of 10 min compared to the MT -group (64 min). Respectively,

Table 2 indicates there being a 78 min difference in the maximum procedure time in favour of the IVT + MT -group. This was caused by a demanding patient case, resulting in an increase in technical difficulty and significantly inflating mean procedure time of MT only -group. This single patient case also explains the considerable 9.0% difference observed in the > 180 min procedure time -category.

No significant difference between the groups can be seen in the minimum (11 min vs. 8 min) or median (53 min vs. 49 min) procedure times.

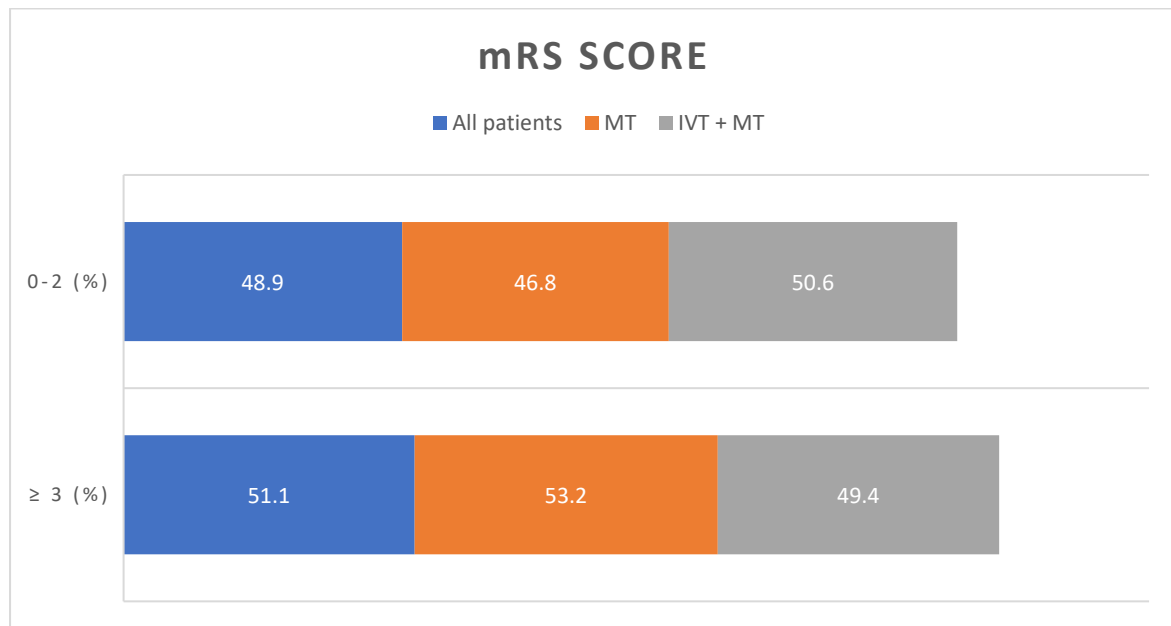
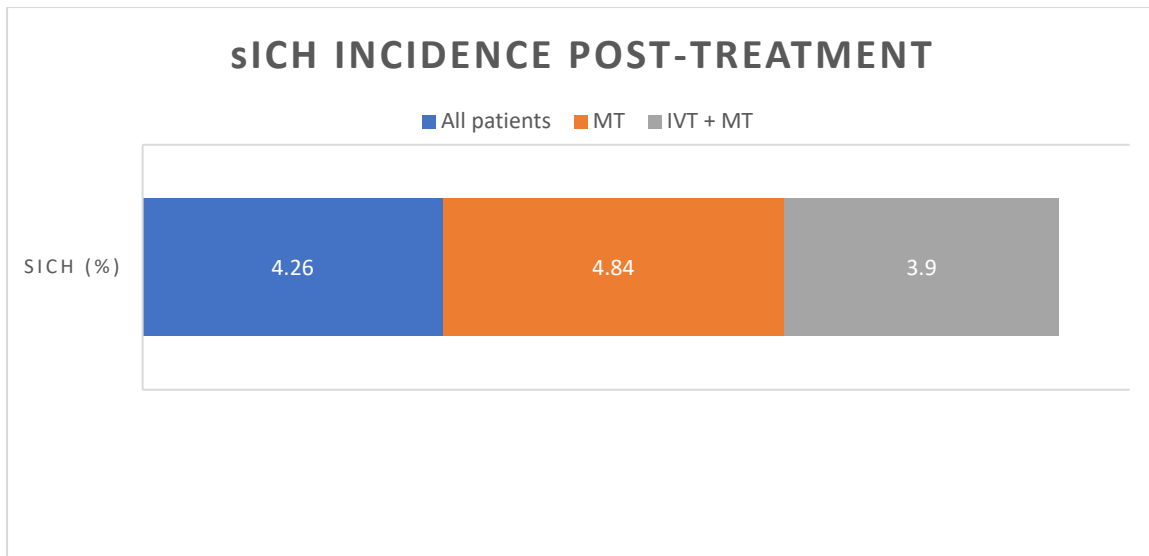


Fig 4. Bar chart showing mRS score 3 months post-treatment

mRS (Modified ranking scale) score is used to determine degree of recovery following acute ischemic stroke and is assessed three months post-treatment. Scores 0-2 indicate adequate (asymptomatic) recovery without the need of external help in everyday life.

Fig. 4 indicates that majority of cases in all patient groups lie within the mRS  $\geq 3$  -group with the largest disparity (53.2% vs. 49.4%) between the MT only and IVT + MT -group. The difference (3.8%) is insignificant and no further conclusion may be drawn as many factors affect mRS score e.g. initial patient condition, patients' subjective view on degree of symptoms etc.





**Fig. 5** Bar chart showing sICH incidence within patient groups

Incidence of symptomatic intracerebral haemorrhages (sICH) was nearly constant between the groups (max. 0.94% difference). Among all patient cases a total of 4.26% were reported to experience sICH.

#### 4. Discussion

The objective of the investigation was to determine does intravenous thrombolysis preceding mechanical thrombectomy affect recanalization results in anterior circulation LVOs. Variables under investigation included recanalization attempts required, type of endovascular device required for recanalization, puncture to recanalization -time (i.e. procedure time), mRS score and sICH incidence.

Percentage distribution within each category was calculated and a minimum difference of 10% was considered the margin for statistical significance. None of the categories obtained the margin of statistical significance, the closest ones being in the procedure times (difference of 9.0%, 5.8% and 5.4%) and mRS score (difference of 3.8%).

As stated earlier, IVT + MT -group consisted of a significantly younger patient cohort (14.4% more  $\leq$  65-year-olds). This reduces probability of health issues affecting treatment results negatively as complex health issues tend to accumulate within the ageing population.

Nevertheless, no significant difference (max. reported difference 9.0%) was present in the procedure times (indication of procedure fluency) as MT only and IVT + MT -groups represented similar distribution within all the subdivision categories.

Earlier studies have shown higher rate of successful recanalization, better functional independence outcome and equal odds of sICH in IVT + MT compared to MT only -groups<sup>10</sup>.

Pienimäki et al. -investigation concluded that MT alone was associated with improved mRS score and was at least non-inferior in the treatment of anterior circulation LVO<sup>11</sup>.

JAMA -investigations demonstrated that MT alone, compared to IVT + MT met the statistical threshold for non-inferiority in mRS score -results<sup>12</sup>. However, wide confidence intervals around effect estimate did not allow conclusion of inferiority<sup>13</sup>.

**Conclusions** based on the current investigation cannot be drawn in favour or against MT alone vs. IVT + MT treatment in recanalization results, as sufficient data displaying its non-inferiority or beneficial position was not obtained. No statistical significance was shown in either group. Further assessment using statistical methods is required in analysing the results.

**Improvements and weaknesses** of the assessment include lack of thorough statistical analyses and relatively narrow patient case cohort (n = 139). As an improvement and extension of the current assessment, patient cohort is to be extended to cover a longer time-period (> 2 years) and include more patient cases.

Investigation data is to be analysed with SPSS software. Group comparisons are to be performed using the *t* test, Chi-squared test, Fisher exact test, Mann-Whitney *U* test, regression analyses and other appropriate means of analyses to determine statistical significance through odds ratio and confidence interval and *p*-value.

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<sup>10</sup> Comparative efficacy and safety of bridging strategies with direct mechanical thrombectomy in large vessel occlusion, Pan et al., 2019

<sup>11</sup> In-Hospital Intravenous Thrombolysis Offers No Benefit in Mechanical Thrombectomy in Optimized Tertiary Stroke Center Setting, J-P. Pienimäki et al., 2020

<sup>12</sup> Effect of Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke, W. Zi, Z. Qiu et al., 2021

<sup>13</sup> Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke, K. Suzuki, Y. Matsumaru et al., 2021